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STUDENT REPORT

ALCOHOLISM: CURRENT MARKER RESEARCH

MAJOR HERBERT R. FINCH

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Presents a review of current alcoholism research efforts directed toward identifying specific markers for alcoholism predisposition or proneness. Genetic, metabolic, neurobiological and blood chemistry marker studies are highlighted in non-technical language. Also included, brief review of major family, twin and adoption alcoholism studies preceding current marker research.		

PREFACE

The role of heredity in alcoholism has been questioned by researchers for many years. Supportive data linking heredity and alcoholism have been accumulated by studying the occurrence of alcoholism in select populations such as families, twins, and adopted children. The statistical implications of such studies caused scientists to begin the search for a unique genetic or biological mechanism that might cause alcoholism in some persons. Such mechanisms are called "markers." Research related to the identity of a marker for alcoholism proneness has moved rapidly in recent years. While researchers have sometimes characterized their past efforts as "looking for a needle in a haystack," the prospects for finding an alcoholism marker and devising a related test for alcoholism proneness have been greatly enhanced in the last five years.

The review that follows offers Military Airlift Command Social Actions personnel an overview of the progress and direction of current alcoholism marker research. If one or more of the research inquiries cited can be validated, an entirely new approach to the early detection and treatment of potential alcohol abusers may be possible.

While source material covering nearly every aspect of alcoholism is abundant, obtaining information regarding current marker research posed an initial problem. By the time relevant commentary on research studies could be located in published volumes, those studies had frequently been superseded by the follow-on work of others. Also, researchers are obviously reluctant to speculate on the possible outcome(s) of their studies currently in progress. The author therefore wishes to express his gratitude to the staff members of both the National Institute on Alcohol Abuse and Alcoholism and the National Clearinghouse for Alcohol Information. Their cooperation and assistance were invaluable in suggesting current relevant sources, helping to obtain initial abstracts and locating source documents not readily available in local libraries or through interlibrary loan.

ABOUT THE AUTHOR

Major Finch is a Military Airlift Command senior navigator with 2600 flying hours in the C-130 Hercules aircraft. In addition to flying assignments with the Military Airlift Command, Air Training Command, and Air Force Systems Command, he has also completed an Air Force Institute of Technology Education with Industry (AFIT/EWI) assignment with the Aerojet Liquid Rocket Company, Sacramento, California. Following AFIT/EWI training, he was assigned to rated supplement duties as a contracting officer at the Sacramento Air Logistics Center, McClellan AFB, California. Prior to attending the Air Command and Staff College, Major Finch was assigned to the 54th Weather Reconnaissance Squadron, Andersen AFB, Guam, as the Assistant Operations Officer. Major Finch obtained his Bachelor of Science degree in Industrial Management from the University of Missouri and a Master of Science degree in Systems Management from the University of Southern California.

TABLE OF CONTENTS

Preface	11
About the Author.	111
CHAPTER ONE - INTRODUCTION	
Background	1
Limitations.	2
Objectives	2
CHAPTER TWO - HISTORICAL REVIEW	
Family Studies	3
Twin Studies	4
Adoption Studies	5
CHAPTER THREE - MARKER RESEARCH	
Marker Studies	7
Genetic Markers.	7
Metabolic Markers.	8
Neurobiologic Markers.	9
Blood Chemistry Markers.	11
CHAPTER FOUR - CONCLUSION	
Summary Remarks.	12
BIBLIOGRAPHY.	13

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Chapter One

INTRODUCTION

BACKGROUND:

In the past, laymen frequently rationalized the otherwise unexplainable physical and mental afflictions of their fellow man as simply resulting from "bad genes." This characterization, a product of innocent ignorance, nonetheless may contain an unwitting basis in fact with respect to alcoholism. A rapidly expanding body of credible evidence exists to support earlier researchers' hypotheses that heredity plays a significant role in predisposing some persons to alcoholism.

Family, twin and adoption studies have been the traditional research methodologies employed to investigate the suspected "family" or hereditary occurrence of alcoholism. Data from such studies have consistently pointed out the higher incidence of alcoholism among family descendants than that observed in the general population. Because the influence of environmental factors versus hereditary influence cannot be totally isolated, researchers have turned in recent years to the pursuit of specific heredity-related markers to identify persons prone to alcoholism.

If a genetic or biological mechanism that triggers alcoholism can be identified, the implications with respect to early identification of potential victims, and prospects for prevention and treatment would be of tremendous benefit not only to the United States Air Force, but to our entire society. The author will highlight current research efforts, either recently completed or currently in progress, dedicated to identifying potential hereditary keys to alcoholism. Although no specific marker has been isolated to date, research progress indicates that this area of inquiry may hold the most promise in the pursuit of potential hereditary causes of alcoholism.

LIMITATIONS

The psychological, social and environmental aspects of alcoholism constitute broad areas of research. Many researchers from these and other scientific disciplines continue to challenge the hypothesis that some aspects of alcoholism may be related to heredity. No attempt has been made to address this continuing controversy. The studies highlighted in this paper are

presented, not to prove or disprove any possible hereditary implications of alcoholism, but to illustrate the types of research that have preceded current alcoholism marker research. As the reader will note, researchers currently involved with marker studies are very cautious in their interpretations of findings.

OBJECTIVE

With these cautions in mind, the author's intent is to provide Military Airlift Command Social Actions personnel with a review of current alcoholism marker research. A representative review of the more frequently cited family, twin and adoption studies is presented first. This information is offered to provide an historical perspective regarding the direction, general findings and limitations of earlier alcoholism research efforts. The reader is encouraged to consult the related sources bibliography for additional references concerning the subjects discussed.

Chapter Two

HISTORICAL REVIEW

FAMILY STUDIES

In 1785 a physician named Benjamin Rush, in his paper, "An Inquiry Into the Effects of Ardent Spirits Upon the Human Body and Mind," voiced his opinion that alcoholism seemed to run in the family. (22:321) Subsequent inquiries in the form of family alcoholism research have consistently documented higher risks for alcoholism among the family members of alcoholics. Nearly forty years ago Dr. Elvin M. Jellinek, a Yale University researcher, studied the "runs in the family" or "like father, like son" hypothesis. His work summarized a group of previous family studies that covered over 4,000 alcoholics. Among his findings was this statistic: 52% of his alcoholic subjects had at least one alcoholic parent. (17:105-114) Numerous family studies since the early work of Jellinek have substantiated a disproportionately high incidence of alcoholism among the descendants of alcoholics. In 1960 Gregory (18:1068) and in 1968 Winokur and Clayton (25:885) reported similar higher familial alcoholism in contrast to general population alcoholism. The norm (or general population occurrence), based on exhaustive studies conducted by Dr. Donald Goodwin and others during the 1970's, is generally accepted to be about 5% in men and 1% or less in women. By way of comparison, family studies consistently show that 25% of the sons of alcoholics and 5% to 10% of the daughters of alcoholics become alcoholics. Stated another way, the child of an alcoholic parent has a four to five times greater probability of becoming an alcoholic than the child of nonalcoholic parentage. (1:72)

Perhaps the most comprehensive recent review of family alcoholism studies was conducted by Nancy Cotton, a clinical psychologist at the Harvard Medical School. She compared the results of 39 family studies that included an aggregate total of 6,251 alcoholic subjects and 4,083 nonalcoholics. Her data, reported in 1979, also showed a 27% average incidence among sons of alcoholics and 4.9% average incidence among daughters of alcoholics. (9:89-116)

Although family studies have repeatedly pointed out the higher risk of alcoholism among descendant family members, they do not differentiate the effects of child environment (i.e. social conditioning) from a potential hereditary cause. Researchers refer to this limitation as the "nurture versus

nature" problem inherent in all family studies. (1:72) In an attempt to address the nurture versus nature question, researchers turned to twin studies.

TWIN STUDIES

Identical twins, by definition, have the same genes and should therefore inherit the same genetically determined traits or characteristics. Conversely, fraternal twins are not more similar or dissimilar genetically than non-twin brothers or sisters, and they should therefore exhibit typical sibling hereditary conditions or characteristics. Thus, the reasoning follows that if identical twins exhibit a shared trait not shared by fraternal twins, then researchers may infer the existence of a genetically linked trait. This phenomena of shared or common traits is referred to as "concordance." (13:406)

In 1960 a Swedish psychiatrist, Dr. Lennart Kaij, studied 174 male twin pairs. His findings showed a 54% concordance for alcoholism among identical twins and a 28% concordance among fraternal twins. (4:59) Two other well-documented twin studies, Partanen's in 1966 (4:59-60) and Loehlin's in 1972 (19:117-120) used a different approach with twin subjects. Their studies focused on frequency and amount of drinking versus a previously identified alcoholic condition. Both studies, however, did show higher concordance among identical twins for the two traits under study. Twin studies have thus provided another statistical inference of possible hereditary involvement in the alcoholic profile. Higher concordance in twins was by no means conclusive, however, and researchers turned to adoption studies as the next step in attempting to separate possible nature and nurture aspects of alcoholism.

ADOPTION STUDIES

Some strongly supportive evidence for a hereditary predisposition to alcoholism that also takes the environmental influence into account has been found in the studies of adopted children. Adoption studies are based on children who are reared by persons other than their biological parents. Theoretically, the environmental (nurture) influence is thus negated because the child of known alcoholic parentage has been separated from that environment. If adopted children then develop alcoholism in numbers greater than the general population, researchers might then infer a probable genetic transmission of alcoholism.

One of the earliest alcoholism-related adoption studies was reported in 1945 by Dr. Anna Roe, a psychologist at Yale University. She and her associate, Dr. Burks, studied a small

group of children who had been placed in foster homes at an early age. One-third of the subjects were children of alcoholics. Ironically, this first study produced negative results: not one of the foster children of alcoholic parentage developed alcoholism. (21:378-393) The Roe study, however, has been criticized due to the small sample size (61) and the lack of follow-up of some of the subjects after age thirty. (6:65) Subsequent adoption studies have countered the Roe findings and yielded strong evidence supporting a genetic alcoholism link that seems to distinguish between environment and heredity. Dr. Marc Schuckit, then a researcher at the Washington University School of Medicine, and his associates reported in 1972 on his study involving adoptees, some with alcoholic natural parents and some with nonalcoholic natural parents. Sixty-two percent who later became alcoholics were the children of alcoholic natural parents. Only 20% of the children of nonalcoholic parents became alcoholic. He found, additionally, that a child with an alcoholic parent had the same risk of becoming an alcoholic whether or not his adoptive parent was an alcoholic. (23:1132-1136)

Another frequently cited adoption study was conducted between 1970-1977 by a team of American and Danish medical scientists headed by Dr. Donald Goodwin of the University of Kansas. In the first phase of the study, ten of the 55 adopted sons of alcoholics were also alcoholics. Only four adopted sons of the 78 nonalcoholics were alcoholics. In the second phase of the study, nearly equal proneness to alcoholism was noted in sons that were raised by their alcoholic parents and those raised by nonalcoholic adoptive parents. (27:59-61) These findings support the earlier Schuckit adoption study.

While the Goodwin study was in progress, Dr. Michael Bohman of the University of Umea in Sweden, conducted a similar adoption study involving 2,000 Swedish adoptees. (7:272-276) Cadoret and Gath reported the results of their similar adoption study in 1978. (8:252-258) The Schuckit, Goodman, Bohman, as well as the Cadoret-Gath studies each produced a significant correlation between the alcoholism of natural parents and the subsequent alcoholism of their adopted-out sons. Adoption studies have thus served to more clearly substantiate a hereditary link to alcoholism. Moreover, adoption studies, in contrast to family and twin studies, more clearly differentiate potential hereditary aspects from environmental influences.

The cumulative results of family, twin and adoption studies support--but do not prove the hypothesis that an inherited component of the alcoholism disease exists. Proving the hypothesis and actually identifying the responsible genetic or biological mechanism(s) are much more complex matters. Family, twin and adoption studies continue to provide useful data for

clinical alcoholism research. At the same time, their findings have resulted in the search for a specific mechanism that triggers alcoholism. Research inquiries of this type are called "marker" studies, and they are the subject of the next chapter.

Chapter Three

MARKER RESEARCH

MARKER STUDIES

Marker studies are scientific attempts to isolate a specific genetic or biological phenomenon as a potential cause of alcoholism. These studies seek a correlation between persons with a trait, condition or characteristic known to be inherited and a coincident high rate of alcoholism. (2:70) Some diseases are known to occur along with others in the same person through direct chromosomal linkage. Persons afflicted with mongolism are high-risk candidates for certain types of leukemia. Similarly, hemophiliacs have a correspondingly high incidence of color blindness. (4:61) Thus persons having certain specific hereditary diseases or traits have been studied as a group to investigate the possibility that they might be "marked" for alcoholism as well. Early efforts in this research area concentrated on the search for genetic markers associated with genetically determined characteristics such as color blindness and blood type.

GENETIC MARKER STUDIES

In 1966 Dr. Cruz-Coke and Dr. Varela reported that their study had linked color blindness, cirrhosis of the liver and alcoholism. They further hypothesized the existence of a sex-linked carrier gene that transmitted alcoholism. (10:1282-1294) Meanwhile, Dr. Failkow and his research associates were conducting a similar study in 1966. Their findings also linked alcoholism, color blindness and cirrhosis, but they found that the color blindness disappeared following the subject's treatment and recovery from severe alcoholism symptoms. (14:584-587)

Blood-typing marker studies have produced similar mixed results. One study published in 1959 showed a high correlation among 939 alcoholics and blood type A. (20:460-461) A similar study in 1973 reported no blood type distribution anomalies among the 448 alcoholic subjects studied. (24:64-70) Subsequent studies by Hill in 1975 (16:981-992) were equally contradictory and therefore nondefinitive regarding a possible blood type

marker for alcoholism. Though these studies, typical of many other early genetic marker efforts, produced inconclusive results, they were the forerunners to an expanding family of marker studies. Currently, researchers are pursuing potential metabolic, neurobiological and blood chemistry markers.

METABOLIC MARKERS

The process of normal metabolism of alcohol by the human body is well known. The liver is the essential organ in the process and produces enzymes that convert alcohol into a number of other products. One of the primary products is a compound called acetaldehyde (AcH). AcH is important because it is responsible for many of the toxic symptoms associated with alcohol: nausea, dizziness, headache and mental confusion as well as potential liver damage. Normally, AcH is further broken down sequentially into acetate and finally into carbon dioxide and water and is eliminated from the body. (30:74) Researchers have speculated that alcoholics might metabolize alcohol differently from nonalcoholics. That speculation has produced some interesting studies in pursuit of a marker related to AcH metabolism.

Dr. Charles Lieber of the Bronx Veterans Administration Hospital conducted a recent study that showed definite differences between alcoholics and nonalcoholics. Alcoholics were shown to have considerably higher blood levels of AcH. Dr. Lieber attributed this excess AcH principally to liver enzyme malfunctions. Something in the alcoholic's biochemical processes apparently inhibited the production of those enzymes required for normal alcohol metabolism. (3:32) Dr. Marc Schuckit, now at the San Diego Veterans Administration Hospital, conducted related research. His data showed that alcoholics metabolize AcH only about one-half as fast as nonalcoholics, and this would account for the abnormally higher AcH levels in alcoholics. (3:33) The obvious question was then raised regarding whether the abnormal AcH level indicated a predisposition to alcoholism or whether the condition was a consequence of heavy long-term alcohol consumption. Dr. Schuckit and his associate, Dr. Rayeses, sought answers to this question by measuring the blood AcH levels of twenty young men after they had consumed specific amounts of liquor. These men were carefully screened subjects who had either an alcoholic parent or sibling (i.e. evidence of familial alcoholism). Their results were contrasted with a control group of twenty subjects of similar age and background, etc. but having no history of familial alcoholism. Their analyses yielded significantly higher levels of blood AcH in the twenty men with a previous family alcoholism history. (29:54-55) Dr. Schuckit has cautioned that the sample size was very small and that technical problems associated with accurate collection of AcH data make the

results tentative. Schuckit and others are currently involved in prospective studies of healthy relatives of alcoholics. If these studies can replicate the earlier tentative findings, a possible marker may be identified regarding abnormal alcohol metabolism as a predictor or precursor of alcoholism. (5:23-48)

Acetaldehyde (AcH) also appears to be a culprit in producing some peculiar chemical reactions in the brain. Some studies have suggested that AcH might combine with other substances in the brain to produce compounds called tetrahydroisoquinolines ("TIQs"). (26:1005-1007) Subsequent research indicates that these TIQ compounds may result in the formation of morphine-like substances that contribute to the alcoholic addiction process. Researchers at the University of Colorado Alcohol Research Center have examined this hypothesis by injecting small amounts of TIQ compounds into the brain tissue of laboratory rats. Some of the rats that had previously avoided drinking alcohol-laced liquids began drinking the liquids in large enough quantities to experience withdrawal symptoms when they were denied the alcohol tonic. (11:55-80) Do some persons metabolize alcohol in a unique way that produces TIQ or other similar isoquinoline compounds? Do these compounds actually cause the physiological dependence associated with alcoholism? No conclusive evidence is yet available, but similar isoquinoline compounds are currently under study at several alcohol research centers including those at the University of Colorado, the University of Texas and the University of Toronto.

In summarizing this series of related alcohol research efforts, one begins to understand the complexities involved in attempting to isolate a single biochemical or metabolic marker. The cause versus effect paradox continues to perplex researchers. Is the key to alcoholism related to an inherited deficient liver that does not break down ingested alcohol properly as Lieber suspected? Can the raised acetaldehyde (AcH) levels of descendants of alcoholics stand alone as a predictor of predisposition to alcoholism? Does the human body produce morphine-like compounds that react with brain enzymes to trigger addiction to alcohol in some persons? No conclusive answers are yet available, and researchers are currently studying all three areas to confirm or negate previous tentative findings. Frequently, tentative findings of scientific studies lead researchers to other potential areas of inquiry. Such was the case when alcohol metabolism studies suggested possible brain chemistry anomalies.

NEUROBIOLOGICAL MARKERS

As indicated above, the complex chemical reactions associated with acetaldehyde, isoquinolines and brain enzymes are not fully understood. Suspecting, however, that brain chemistry

is involved, scientists are now studying brain wave patterns to see if a neurobiological marker can be found. In these studies, electroencephalograms (EEGs) - or brainwave patterns - of both high and low risk subjects are compared. The high risk subjects are those persons with a family history of alcoholism. (As previously noted, family, twin and adoption studies all tend to corroborate the much higher incidence of alcoholism among those with alcoholic family members.)

One such study was conducted recently at the Salk Institute, Laboratory of Neuropsychology in San Diego, California. The researchers hypothesized simply that the EEGs of high and low risk persons would be different. Normal (non-abusive) drinkers were examined; some with and some without a family history of alcoholism. Three groups of ten subjects each were given either a measured amount of alcohol or a nonalcoholic beverage, and their EEGs were recorded as they proceeded to perform a series of vigilance tasks, e.g. correctly identifying moving targets on a television screen. As hypothesized, significant characteristic anomalies (decreased P3 wave amplitudes) were observed among the high risk subjects. Their brain wave patterns not only showed a consistently reduced P3 wave amplitude, but their reaction times were significantly slower than their low risk counterparts. More importantly, these phenomena were observed whether the high risk subjects had been given the alcoholic beverage or not. The results, therefore, suggest that the brain functions of high risk subjects are different from those at low risk. (12:7900-7903) Dr. Henri Begleiter of the Downstate Medical Center in Brooklyn, New York, is currently engaged in similar research. His data show a 30-40% occurrence of the same abnormal P3 wave anomaly among children of alcoholics. He suspects that this anomaly may represent a predisposing factor for alcoholism. (31:Nova)

A related EEG study was conducted recently by scientists at the University of Southern California's Social Science Research Institute. They knew from previous researchers' findings that one characteristic of the EEG called "fast activity" had been previously shown to be genetically transmitted. Therefore, if this EEG anomaly was also characteristic of alcoholics (a hypothesis), then the children of alcoholics should exhibit this same "fast activity" in their EEGs. The test group consisted of 265 children from eleven to thirteen years of age. Some were children of alcoholics and some were not. The results confirmed the existence of the fast EEG pattern in the young children of alcoholics versus the normal EEG pattern in low risk children tested. Previously, researchers who noted the fast EEG activity in known alcoholics were unable to determine if the characteristic was a consequence of long alcohol abuse or a condition that existed prior to the alcoholic condition. Given the results of this test with pre-drinking aged children, researchers are now cautiously speculating that they may have the

basis for a predictive test of predisposition to alcoholism. Further evidence to help validate or invalidate these tentative findings will be accumulated as researchers monitor the subjects of this study over a period of years. If a significant number of the high risk fast EEG activity subjects subsequently develop alcoholism, a neurobiological marker for early detection of alcoholism predisposition may be confirmed. (15:404-407)

BLOOD CHEMISTRY MARKERS

Dr. Ralph Ryback and his associates at the National Institute on Alcohol Abuse and Alcoholism are using a sophisticated, mathematical modeling technique and computer technology to establish a blood chemistry profile or "print" to identify alcoholics. Their blood chemistry model has been able to accurately discriminate between severely ill alcoholics, moderate alcohol abusers and members of a nonalcoholic control group. (30:74-75) While these blood chemistry test results have not produced a marker for alcoholism, they offer two promising benefits. Continued refinement of such tests should allow earlier positive identification of persons who are on the way to becoming alcoholics as well as those who are already in the more severe stages of alcoholism. Perhaps more importantly, the continued refinement of blood chemistry technology and evaluation may help researchers to understand the significance of a blood chemical known as "2,3 butanediol".

A Harvard epidemiologist, Dr. David Rustein, along with biochemists from both the National Institute on Alcohol Abuse and Alcoholism and the Center for Disease Control, have recently reported elevated levels of 2,3 butanediol in their alcoholic subjects' blood samples. Almost 80% of the alcoholics they studied exhibited this blood oddity. Only one of their nonalcoholic control subjects had the same blood irregularity. The 2,3 butanediol appears after alcohol is ingested. Researchers suspect this occurrence may be further evidence that alcoholics metabolize alcohol differently from nonalcoholics. Laboratory rats in previous experiments have produced this chemical when their normal alcohol metabolism routes have been deliberately blocked. No such studies on human subjects have been conducted, and scientists are not certain that 2,3 butanediol is not a by-product of human alcohol metabolism. More definitive research is necessary to be able to confirm or deny that elevated levels of 2,3 butanediol in the blood is a marker for predisposition to alcoholism. It is interesting, but unscientific, to note that the one nonalcoholic control subject who had an elevated 2,3 butanediol level was later diagnosed and treated for alcoholism. (28:180)

Chapter Four

CONCLUSIONS

SUMMARY REMARKS

The hypothesis that alcoholism can be positively linked to heredity remains unproven. Cumulative research data, however, tend to support the hypothesis. Family studies consistently produce data showing an increased incidence of alcoholism among the descendants of alcoholics. Twin studies have attempted to isolate possible hereditary factors from environmental conditioning factors. The higher incidence of alcoholism between identical twins versus fraternal twins is viewed as an additional indication of a hereditary connection. Adoption studies have attempted to further differentiate between possible genetic and environmental factors. The cumulative implications of family, twin and adoption studies have opened up new areas of inquiry including the pursuit of a marker for the alcoholism disease.

Marker studies appear to hold the most promise for early identification of those persons prone to alcoholism. As noted, early efforts to link alcoholism with known heredity-related diseases such as colorblindness or blood type were contradictory. More recently, researchers have been concentrating on biological processes including human alcohol metabolism, unique brain wave phenomena and blood chemistry peculiarities. As yet, no single marker for alcoholism can be claimed. The tentative findings of possible markers will require several years of study and analysis to replicate, clarify and confirm early indications. Researchers in the field of alcoholism are cautiously using terms such as "proneness" and "predisposition" regarding current marker findings. No tests are yet available to clearly identify those individuals who may be predisposed to alcoholism. If the rapid progress that is being made in marker research is sustained, then such tests may be forthcoming. Professionals associated with the identification, treatment and care of alcohol abusers should be closely monitoring the rapidly advancing testing aspect of alcoholism marker research. If prospective tests for alcoholism proneness are validated, their potential use will be tempered by legal and ethical considerations. Given the pace, progress and convergence of current research, it may not be too soon to begin contemplating the "when, how and why" questions regarding the administration of alcoholism proneness testing.

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